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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,679	11/14/2003	Denise Faustman	00786/428002	2917

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EXAMINER	
JUEDES, AMY E	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,679	FAUSTMAN, DENISE	
	Examiner	Art Unit	
	Amy E. Juedes, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *1-11,16,17,19 and 22-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-15, 18, 20-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *notice to comply*.

DETAILED ACTION

1. Applicant's election without traverse of group 23, drawn to a method for diagnosing autoimmune disease comprising contacting leukocytes overexpressing IFN-gamma receptor with an antibody agonist of TNF-alpha receptor, claims 12-15, 18, and 20-21, in the reply filed on 12/26/06, is acknowledged.

Claims 1-11, 16-17, 19, and 22-55 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 12-15, 18, and 20-21 read on the elected invention and are being acted upon. It is noted that the claims are only being examined as they read on the elected group of diagnosis employing an antibody agonist of TNF-alpha receptor.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 for the reason(s) set forth below:

The specification fails to disclose the SEQ ID NOs: for the amino acid sequences in Fig. 3.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 13 is unclear and indefinite since it recites myasthenia gravis as the autoimmune disease twice, in lines 14 and 21.

B) Claim 15 is indefinite in the recitation of FasL, TNF, IL1, IL-6, IL-12, and IFN-gamma as being "chemokines". Chemokines are a family of chemotactic cytokines of small size sharing certain structural characteristics. None of the recited molecules in claim 15 are chemokines. Additionally, claim 15 is

indefinite in the recitation of a leukocyte that "overexpresses" a receptor. The term "overexpress" is entirely relative. Cells express different levels of different receptors at different times during their life cycle. For example, T cells upregulate FasL expression after activation. Said activated T cells might "overexpress" FasL compared to resting T cells. Thus, given the relative nature of the term "overexpress", the metes and bounds of the claims cannot be established.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-15, 18, and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of "compounds" that decrease the viability of leukocytes and "TNF-alpha receptor agonists".

The instant claims are drawn to a method of diagnosing autoimmune disease comprising contacting cells with a "compound" that decreases the viability of leukocytes. Thus, the claims might encompass contacting with a virtually unlimited number of compounds that induce cell death, including antibodies, nucleic acid molecules, small molecules, toxins, or even bleach or azide. It is clear that the classes of compounds encompassed by the claims have no structural similarity. Furthermore, while the compounds are limited to those that decrease leukocyte viability, this might still encompass compounds that vary considerably in terms of their function. For example, the compounds might act by triggering a specific death receptor such as Fas, or might alternatively act by inducing activation induced cell death. The compounds might also function in a non-specific manner by being generally cytotoxic. While the specification does disclose on page 6 several examples of compounds that can be employed in the claimed method, they are

not sufficiently representative of the virtually unlimited number of structurally and functionally different compounds encompassed by the claims.

Furthermore, even when the compounds are limited to "TNF-alpha receptor agonists", the claims still encompass a broad range of structurally different molecules. For example, the claims encompass agonists that are antibodies, small molecules, natural or mutant ligands, peptides, etc. Furthermore, the agonists might function to stimulate different TNF-alpha receptors (i.e. TNFR1 or TNFR2). Thus, the claims encompass structurally different agonists that might function to stimulate structurally and functionally different receptors. The specification only discloses antibody agonists of TNF-alpha receptor and TNF-alpha. The disclosure of the natural ligand of TNF-alpha receptors and antibody agonists is not representative of the broad range of structurally different agonists encompassed by the claims. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

9. Claims 12-15, 18, and 20-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method would function to diagnose autoimmune disease as broadly claimed.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, *in re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the

invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable.

The instant claims are drawn to a method of diagnosing autoimmune disease, or a predisposition to said disease, comprising contacting a blood sample with a compound that decreases leukocyte viability. A diagnosis of autoimmune disease is made by detecting a preferential decrease in the viability of autoimmune leukocytes, compared to those of normal leukocytes. Thus, the asserted mechanism by which the claimed method functions is that leukocytes from patients with autoimmune disease are more susceptible to cell death. However, the instant claims encompass an overly broad method of diagnosing a wide range of different diseases with different etiologies and pathological mechanisms. For example, the claims encompass diagnosing disease ranging from organ specific autoimmune diseases such as diabetes or multiple sclerosis, to immune deficiencies such as primary agammaglobulinemia, or infectious disease such as hepatitis, or even other diverse diseases including chronic fatigue syndrome, pulmonary fibrosis, or alopecia. It is unlikely that a single diagnosis method could be effective for such a broad range of different diseases. For example, the instant claims encompass diagnosing alopecia by detecting a decrease in leukocyte viability. However, peripheral blood lymphocytes from alopecia patients display increased resistance toward apoptosis compared to healthy controls (see Zoller et al.). Likewise, multiple sclerosis is associated with impaired apoptosis of PBMCs compared to controls (see Macchi et al.). Additionally, PBMCs from patients with rheumatoid arthritis display reduced apoptosis compared with healthy controls (see Szodoray et al. Fig. 2 in particular). Therefore, the instant method that detects a detects a decrease

in leukocyte viability would be unlikely to be effective in diagnosing alopecia, multiple sclerosis, or rheumatoid arthritis, which are diseases known to be associated with increased resistance of lymphocytes toward cell death.

Additionally, even though autoimmune diseases such as type I diabetes are known to be associated with an increase in TNF-alpha mediated apoptosis (see Hayashi et al.), the instant claims encompass measuring cell viability after contact with any "compound" or any TNF-alpha receptor agonist. For example, while leukocytes from mice predisposed to diabetes might be more sensitive to TNF-alpha mediated apoptosis, they are resistant to apoptosis induced by cyclophosphamide (see Colucci et al.). Thus, not all compounds that induce cell death will function in a method of diagnosing autoimmune disease. Furthermore, even if the claims are limited to TNF-alpha receptor agonists, this still encompasses compounds that stimulate functionally different receptors. There are two immunologically distinct TNF-alpha receptors (TNFR1 and TNFR2, see Tartaglia et al.). While TNF-alpha might induce enhanced apoptosis of leukocytes from mice predisposed to diabetes (see Hayashi et al.), it is known that antibody agonists of TNFR1 and TNFR2 mediate distinct activities depending on the experimental conditions. For example, anti-TNFR1 antibodies mediate apoptosis in PBMCs from healthy controls, but do not cause increased apoptosis in PBMCs from autoimmune arthritis patients (see Szodoray et al.). In contrast, antibodies specific for TNFR2 do not mediate cytotoxicity, but rather induce proliferation (see Tartaglia et al., Fig. 1 and Fig. 2, in particular). Additionally, neither TNFR1 nor TNFR2 antibodies induce cell death in T cell blasts, although a combination of anti-TNFR1 and anti-TNFR2 antibodies is comparable to TNF-alpha in inducing T cell death (see Sarin et al., page 3717). These studies demonstrate that the effect of a particular TNF-alpha receptor agonists is unpredictable, and depends on the cell subset, activation status, and specificity of the agonists (i.e. TNFR1 vs. TNFR2).

Based on the state of the art, the instant specification must provide a sufficient and enabling disclosure commensurate in scope with the method of the claims. However, the only examples provided by the instant specification involve contacting blood samples of type I diabetic patients with TNF-alpha, followed by measuring T cell viability. This specific example demonstrates that in humans, T cells from type I diabetics exhibit an increase in cell death compared to

controls. The specification further demonstrates that in NOD mice predisposed to diabetes, T cells exhibit increased cell death after culture with TNF-alpha compared to controls. However, no examples are provided that demonstrate that the method can function to diagnose any other organ specific autoimmune diseases, much less the wide range of different pathological conditions and diseases encompassed by the claims. Furthermore, no examples are provided that demonstrate that disease can be diagnosed by contacting with other compounds, including antibody agonists of the TNF-alpha receptor. Accordingly, the method as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy E. Juedes, Ph.D.
Patent Examiner
Technology Center 1600

3/3/07
G.R. EWOLDT, PH.D.
PRIMARY EXAMINER

Notice to Comply	Application No. 10/713,679	Applicant(s) FAUSTMAN ET AL.	
	Examiner Amy E. Juedes, Ph.D.	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: see attached office action.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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